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3/27/03

DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

(Under 37 CFR ə 1.63; includes reference to PCT International Applications)

FROMMER LAWRENCE & HAUG LLP

File No.:

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention ENTITLED: LANTIBIOTIC, the specification of which ☐ is attached hereto ☐ was filed on as ☐ United States ☐ PCT Application No. PCT/NZ00/00197, with amendments through (if applicable, give details).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT International application(s) designating at least one country other than the United State of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT International applications designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) on which priority is claimed:

Prior Foreign/PCT Application(s) [list additional applications on separate page]:

Country (or PCT)	Application Number:	Filed (Day/Month/Year)	Priority Claimed: Yes	No
New Zealand	500261	12 October 1999	X	☐

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States application listed below:

_____ _____
(Application Number) (Filing Date)

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. (or U.S.-designating PCT) Application(s) [list additional applications on separate page]:

U.S. Serial No.:	Filed (Day/Month/Year)	PCT Application No.	Status (patented, pending, abandoned)
	12 October 2000	PCT/NZ00/00197	Pending

I hereby appoint , Registration No. , and Frommer Lawrence & Haug LLP, or their duly appointed associate, my attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to file continuation and divisional applications

US form

DECLARATION FOR PATENT APPLICATION
AND POWER OF ATTORNEY (Under 37 CFR § 1.63)

FLH Docket No.

thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therewith, and specify that all communications about the application are to be directed to the following correspondence address:

, Esq.
c/o FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, NY 10151

Direct all telephone calls to: (212) 588-0800
to the attention of:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

INVENTOR(S):

Signature: _____ Date: 25/11/02
Full name of sole or first inventor:
JOHN ROBERT TAGG
Residence: 39 Braeview Crescent, Dunedin, New Zealand
Citizenship: Australia

Signature: Karen P. Dierksen Date: Oct. 11, 2002
Full name of 2nd joint inventor (if any):
KAREN PATRICIA DIERKSEN
Residence: c/o- 3450 SW Campus Way, Corvallis, OR 97331-8539,
United States of America
Citizenship: United States

Signature: _____ Date: 10/9/02
Full name of 3rd joint inventor (if any):
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Residence: 9 Bolton Avenue, East Didsbury, Manchester M19 1RP,United Kingdom
Citizenship: Britain

Post Office Address(es) of inventors [if different from residence]:

NOTE: In order to qualify for reduced fees available to Small Entities, each inventor and any other individual or entity having rights to the invention must also sign an appropriate separate "Verified Statement (Declaration) Claiming [or Supporting a Claim by Another for] Small Entity Status" form [e.g. for Independent Inventor, Small Business Concern, Nonprofit Organization, Individual Non-Inventor].

US form

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of
TAGG et al.

Atty. Ref.: 512585-2001

Serial No. 09/913,763
Filed: 12 October 2000
For: LANTIBIOTIC

Examiner: Michael V Meller

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Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

DECLARATION

Sir:

I, John Robert Tagg, do hereby declare and state that:

1. I am an Australian citizen and live in Dunedin, New Zealand.

2. I am a Professor of Microbiology at the University of Otago, Leith Street, Dunedin, New Zealand. I am a scientific consultant to Blis Technologies Limited and my brief curriculum vitae is attached as Exhibit 1.

3. I am an inventor of the above-identified patent application.

4. I have read the Office Action on this application dated 14 November 2002 and each of the citations referred to in that report.

5. I advise that we have obtained and sequenced a structural gene of a variant Salivaricin B protein from *Streptococcus mitis*. The variant exhibits a single amino acid change from arginine to histidine at residue 13. The sequence comparison is shown as follows:

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GGTGGTGGAGTAATCCAAACCATTTCACACGAATGTCGTATGAACTCATGGCAGTTCTTGTTTACTTGTTGCTCTTAA K12
 G  G  G  V  I  Q  T  I  S  R  E  C  R  M  N  S  W  Q  F  L  F  T  C  C  S  *

GGTGGTGGAGTAATCCAAACCATTTCACACGAATGTCATATGAACTCATGGCAGTTCTTGTTTACTTGTTGCTCTTAA Variant
 G  G  G  V  I  Q  T  I  S  H  E  C  M  H  N  S  W  Q  F  L  F  T  C  C  S  *
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6. I further confirm that the variant exhibits substantially the same profile of activity as the Salivaricin B protein obtained from streptococcus K12. The activity profile is provided in Exhibit 2. Comparison is made with a *Salivaricin B* producing K12 equivalent. The *Salivaricin B* encoded by K12 and this variant is the same. The nucleotide sequences differ only in the codons for Arg in position 13. K12 has CGC and the reference strain has CGT. The reference strain was used because, unlike K12, it produces only *Salivaricin B*, not *Salivaricin A* as well. For comparative purposes *Salivaricin A* production needed to be excluded.

7. It is also my belief that variants of this short 25 amino acid sequence can be synthesised (for example, as taught in Ross et al, Applied and Environmental Microbiology, Vol 59, No. 7, July 1993, pp 2014-2021; and Wakamiya, T. et al.; Nisin and Novel Lantibiotics, Jung, G. and Sahl, H-G eds, ESCOM, London, pp 189-203), and the activity readily determined using the activity detail provided in the specification accompanying the present application. Synthesising, deletion, insertion, and substitution variants is within the capacity of a skilled worker in this area.

8. I have also read each of the five citations referred to by the Examiner. I do not believe that the peptide presently claimed, nor the organisms producing same, are described in any of these citations for the following reasons:

(i) Caufield et al. (US 5,872,001) discloses a 27 amino acid sequence which is matched against SEQ ID NO:3 as follows:

Tagg SEQ ID NO:3	1 __GGGVIQTISHECRMNSWQFLFTCCS	25
Caufield SEQ ID NO:8	25 CGGSGVIHTISHECNMNSWQFVFTCCS	51

The two sequences as compared in this way have less than 76% identity. There is nothing in this document which teaches or motivates the production of the present 25 amino acid antibacterial protein or variants of it.

(i) Indeed, a person working in this field based on what was known would have assumed that the N-terminal amino acid sequence in Caufield was essential to function. The importance of the N-terminus can be seen in Jack and Tagg, 1991, Nisin and Novel Lantibiotics, Jung, G. and Sahl, H-G eds, pp 71-179, ESCOM, Leiden and Chan et al.,

1993, J. Biochem 291: 23-27. The former teaches a lantibiotic SA-FF22 and a variant thereof as follows:

SA-FF22 GKNGVFK_I_HE_HLN__AFLA
Variant ____VFK_I_HE_HLN__AFLA

The variant with the first four amino acids missing has no biological activity.

The latter reference teaches a naturally occurring subtilin (a lantibiotic) with a succinylated N-terminus. This variant was also reported to have appreciably lower antibacterial activity than the unsuccinylated sequence. Accordingly, the expectation for the Caufield sequence would have been that removing or altering the N-terminus sequence would have destroyed or reduced activity of the sequence. A worker in this field would therefore have been motivated to maintain the full N-terminus sequence, rather than to produce an N-terminal truncated variant.

(ii) The Ross publication teaches *Salivaricin A* protein obtained from *Streptococcus salivarius* 20P3. This is a 51 amino acid pre-peptide which is cleaved to give a biologically active 22 amino acid residue. This peptide has a distinct length, molecular weight, sequence and properties. It is bacteriostatic rather than bacteriocidal. Accordingly, this reference teaches a different protein, with different activity, from a different strain of microorganism.

(iii) Based on my knowledge of *Streptococcus salivarius* strains, I can advise that of some 780 *S. salivarius* strains tested to date, to my knowledge only 1.54% produce the antibacterial protein having SEQ ID NO:3 or a protein having greater than 80% identity with same.

(iv) As taught in the Tagg et al. paper (of which I am an author), of the disclosed 1450 *S. salivarius* strains, 45% of them have been shown to be BLIS positive, and 12 different BLIS types have been identified. These microorganisms therefore exhibit significant diversity in the proteins that they produce. It is not inherent that any *Streptococcus salivarius* will produce the protein presently claimed. Given that only 1.54% of the 780 strains tested to date have been shown to produce the protein presently claimed, it is highly unlikely that any given *S. salivarius* strain will produce the presently claimed protein. Moreover, the analysis presented in the Tagg paper is based on a study of a non-public *S. salivarius* library.

(v) The Sanders et al. paper discloses *S. salivarius* strain K58. This is a different strain from K12 in the present specification. The antibacterial disclosed as being produced is enocin with a molecular weight of less than 200 Da. This is likely to be 2 to 3 amino acids. In comparison, our protein has a molecular weight of 2733 Da. It is a 25 amino acid protein. There is no similarity between these sequences. Enocin is a very much shorter molecule with entirely different properties.

(vi) Matsushiro et al. discloses the production by *S. salivarius* strains of the enzyme dextranase and claims that this strain may impact on dental caries by reducing the glucan (water-insoluble polymer) component of plaque, thus leading to lessened plaque accumulation. There is no suggestion anywhere at all of bacterocin or BLIS activity by the strain. So, it is a mechanism of potentially reducing the levels of plaque and, indirectly of therefore reducing the levels of dental caries/associated bacteria by limiting the accumulation of water-insoluble polymer in dental plaque. There is no description of any BLIS production, let alone the protein we presently claim which achieves targeted killing of bacteria. The patent does not identify either a relevant BLIS producing strain, or BLIS produced by same, nor how to identify such a strain or protein.

(vii) Kawai et al. (US 4,710,379) discloses organisms which can be used to stimulate the growth of useful lactic acid microorganisms in the gut. What is described are anti-carriogenic or anti-periodontic effects associated with some bacteria. There is no mention of *S. pyogenes* as a target, nor is there any characterisation of inhibitory agents. Most importantly, they make no mention of *S. salivarius*. The bacteria they list is "*Lactobacillus salivarius*" which is a member of an entirely different genus of bacteria (gram-positive rod shaped), whereas streptococci are gram-positive coccus-shaped. The bacterial species are therefore quite different. Not only is no *S. salivarius* disclosed, there is no teaching or isolation of any proteins, let alone a BLIS protein or the specific protein of the present invention.

(viii) In conclusion, none of the references cited contains a description of the organisms of the present application, the protein of the present invention, nor any indication as to how to find the strains or proteins which exhibit the antibacterial properties of SEQ ID NO:3.

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

John Robert Tagg

12 March 2003

Date

Attachment: Curriculum Vitae